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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,787	02/11/2000	Laurent Coen	03495.0187	4369

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EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/501,787	COEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-11,31 and 33-37* is/are pending in the application.

4a) Of the above claim(s) *12-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,31 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant is notified that the finality of the previous Office Action (Paper 13) is withdrawn in view of the teachings of Halpern, JL, et al, Infection and Immunity 58(4)1004-1009, April 1990. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicant can request a refund for the associated fees or leave it as credit for future appeals.

Claims 1-5, 8-37 Claims 12-30, 32, withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Further, claims 1-5 and 8-11 are being examined only to the extent that the claims read on the in vivo delivery of a composition comprising fragment C of tetanus toxin plus at least 11 amino acids of fragment B. Further, claims 8-11, 31, 33-37 are being examined to the extent that they read on SMN protein, as set forth previously.

Withdrawn Rejections:

All prior rejections were based on the applicability of the teachings of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987 to the claims. Fairweather et al. teach a polypeptide (pTET18) comprising the C-fragment of tetanus toxin and 121 amino acids of the B-Fragment, for use as an immunogen in mice. Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, however, provide evidence that one of ordinary skill in the art, at the time the instant invention was made, would be dissuaded from using the polypeptide taught by Fairweather et al. for the purpose of binding to neuronal cells. At page 1007, Col 2, 3rd paragraph, Halpern specifically refers to the Fairweather polypeptides (pTET11 and pTET18)

and comments that no functional properties have been reported for them and also that the polypeptides are insoluble and implies that, therefore, the polypeptides would not be useful for binding to neuronal cells. Halpern further speculates that the inclusion of the additional heavy chain sequence resulted in an altered conformation that may have made the C-fragment insoluble. It should be noted that pTET11 does not contain any H-fragment amino acids and consists of the last 441 amino acids of the C-fragment fused at its N-terminus to a large portion of the trpE protein. Never-the-less Halpern teaches the desirability of including a short portion of the H-fragment (e.g. 9 amino acids) when using the C-fragment for binding to neuronal cells, see page 1007, col 2, paragraph 4 and also the second paragraph of the DISCUSSION on page 1007 for a description of the Halpern protein.

New Rejections

Claims 1-8, 11, 31, 34, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990.

U.S. Patent No: 5780024 discloses an in vivo method for delivery (e.g. intramuscular, see col 4) of a composition (SOD:Tet451), comprising a the tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see col 1). Further, U.S. Patent No: 5780024 disclosed

that the method can be used in the treatment of neurodegenerative diseases of the CNS (see col 1 for example).

U.S. Patent No: 5780024 discloses that the tetanus toxin C fragment used in the method of delivery can include additional amino acids, see col 6, as a matter of routine optimization of operating perimeters; yet U.S. Patent No: 5780024 does not disclose, specifically, that the C-fragment should contain at least 11 amino acids of the B-fragment nor that the there should be exactly 11 (claim 37). U.S. Patent No: 5780024 disclose embodiments having 2 or 8 additional amino acids (col 6) and indicate that more or less are encompassed by the invention, and can be added, particularly as a matter of convenience in the cloning process, e.g. col 6, lines 37-40. However, Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of

routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the invention disclosed in U.S. Patent No: 5780024 The motivation to do so was provided by both U.S. Patent No: 5780024, wherein it was taught that additional amino acids of the B-fragment may be added to the C-fragment as a matter of routine optimization, and Halpern et al. who teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the invention of U.S. Patent No: 5780024, e.g. see col 1, lines 64-col 2 line 9 of U.S. Patent No: 5780024 .

Applicant's arguments, as they may pertain to the instant rejection, are addressed below. At page 8 of the Brief, Applicant argues that the '024 patent only speculates that the protein would be transported trans-synaptically and that Applicants were the first to demonstrate this. This argument has been fully considered but not deemed persuasive. One would have no reason to doubt the assertions of the '024 patent; Applicant has provided no such reasons.

Applicant's arguments regarding the distinction between retrograde and transynaptic transport have been thoroughly discussed previously. Applicant has provide no reasons as to why one would doubt the assertions of the '024 patent. At page 16 of the Brief, Applicant alleges that the specification at pages 2-4 teaches that others have failed to show trans-synaptic transport. This argument has been fully considered but not deemed persuasive. Although the staining of second order neurons was week, Kuypers et al, it could be detected in certain synaptically connected neurons (see the instant specification at page 3 bridging page 4. This statement in the specification is a clear admission that the C-terminal fragment was trans-synaptically transported.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to claims 1-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990.

Claims 9 and 10 require a method as claimed in claims 6-8 as discussed above, yet claims 9 and 10 also require that the composition comprise at least two of said second molecules (claim 9) or that the said second molecule be located upstream of the tetanus toxin fragment. Fishman et al. teach that a second biologically active molecule can be conjugated to the tetanus C-fragment multiple times throughout the length (upstream or downstream) of the C-fragment (see page 313, middle paragraph and Figure 1, lanes 2 and 3). Therefore, it would be an obvious matter of routine optimization of operation parameters to incorporate at least two biologically active molecules to the C-fragment of the tetanus toxin, wherein at least one was associated upstream of the C-fragment, as taught by Fishman et al. when practicing the method of U.S. Patent No: 5780024 with the motivation to add amino acids of the B-fragment as taught by Halpern et al., as discussed above. The motivation to do so is provided by Fishman et al. who teach that multimeric complexes are desirable (page 13 middle paragraph). Fishman et al., also provide the artisan with a reasonable expectation of success because Fishman et al. teach that the large size of such complexes does not interfere with the uptake of the complexes into neurons (page 322, middle paragraph).

Applicant's arguments regarding the '024 patent have been discussed above. At page 17 of the Brief, Applicant argues that Fishman et al. neither teaches or suggests the in vivo

transsynaptic transport of a fusion protein containing a tetanus toxin fragment. This argument has been fully considered but not deemed persuasive. Applicant's attention is drawn to page 323 of Fishman et al., wherein Fishman et al clearly state that linkage of the C-fragment of tetanus toxin to another protein may "enhance the stability of a chosen protein within the CNS as well as promote its spread by transsynaptic transport", see page 323, 1st full paragraph.

Claims 1-8, 11, 31, 33-36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948.

Applicant's elected species of SMN (claim 8) is not taught by either U.S. Patent No: 5780024 or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Halpern and by U.S. Patent No: 5780024, as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases

(see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

Applicant's arguments regarding Patent No: 5780024 have been addressed above.

Claims 1-8, 11, 31, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995, in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990.

Francis et al. disclose an in vitro method for delivery of a composition (SOD:Tet451), comprising a tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein, absent evidence to the contrary, the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see page 15434). Francis et al. did not use the method for in vivo delivery, however they proposed to do so (see the Abstract, for example). Further, Francis et al disclosed that the method could be used in the treatment of neurodegenerative diseases of the CNS (15434 see col 1 for example). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to with reasonable expectation of success to use the in vitro method of delivery disclosed by Francis et al. for in vivo delivery, as required by the instant claims. The motivation to do so was provided by Francis et al. who state the tetanus toxin has a well documented capacity for neuronal binding and internalization. In particular when administered systemically or intramuscularly to animals, the toxin is taken up selectively by motor neurons in the brain stem and spinal chord. The C-fragment retains these

properties without the toxic domain (see 15434 see col 1). Further, Francis et al. hypothesize that their disclosed fusion protein could increase the delivery of the SOD-1 protein to the central nervous system in general and motor neurons in particular, potentially providing effective enzyme therapy to neurons (see 15434 see col 1).

Francis et al. disclose that it is the C-fragment of tetanus that provides for neuronal binding and internalization without toxicity, yet Francis et al. do not disclose, specifically that the C-fragment should contain at least 11 amino acids of the B-fragment. Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the method taught and proposed by Francis et al. The motivation to do

so was provided by Halpern et al. who teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the method taught and suggested by Francis et al..

Applicant argues that the selective uptake of the tetanus toxin by motor neurons in the brain stem and spinal cord refers to in vivo retrograde axonal transport - not in vivo transynaptic transport. Applicant argues that Francis et al. do not disclose in vivo transynaptic transport. This argument has been fully considered but not deemed persuasive. Referring to the uptake of the fusion protein by motor neurons, at page 15441, col 1, last sentence of the first full paragraph, Frances et al. teach "through this pathway, the hybrid protein could access other central nervous system neurons as well, given the ability of TTC to undergo retrograde trans-synaptic transfer".

Claims 6-8, 11, 31, 33, 35, 36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948.

Applicant's elected species of SMN (claim 8) is not taught by either Francis et al. or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of

success to modify the C-fragment of tetanus toxin as taught by Halpern et al. and by Francis et al., as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

Applicant's arguments regarding Francis et al. have been addressed above.

Conclusion

No claims are allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

April 12, 2004

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